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SERIA III TOMUL XIV MEM. 11

A CENTRAL MECHANISM FOR THE REGULATION OF POTASSIUM-CALCIUM BALANCE

BY

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MONITORUL OFICIAL ȘI IMPRIMERIILE STATULUI IMPRIMERIA NAȚIONALĂ
DEPOZITUL GENERAL CARTEA ROMÂNEASCĂ B-DUL ACADEMIEI, 3—5
BUCUREȘTI
1939

MEMORIILE SECȚIUNII ȘTIINȚIFICE

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A CENTRAL MECHANISM FOR THE REGULATION OF POTASSIUM-CALCIUM BALANCE [1])

BY

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Pending the publication of several extensive reports dealing with experiments relating to the ionic balance in the body, which I have performed alone or with different collaborators from 1927 to 1938, it seemed desirable to review briefly in this paper the most important results.

I

1927—1929

In collaboration with *Florica Gr. Popa*

A) *Facts observed.*

1. « Motor and sensory roots of brachial plexus (in pigeons) severed. Sympathetic nerves to the wing excited faradically for 2—5—10 minutes, one minute off and one on. Blood collected (from the aorta into 3.8 p. c. sodium citrate, 2: 1, and placed on ice-chest for 24 hours). This yields what may be called „*Somatic serum*" » [2]).

(Physiol. Soc. Proceed. December 5. 1928). (Fig. 3).

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[1]) The whole series of experiments was helped by a Grant of the Rockefeller Foundation of New York.

[2]) More details in the paper: Gr. T. Popa: *The changes in the blood serum of bird and mammal as a result of (I) stimulation of somatic and sympathetic nerves and (II) injection of salts of potassium and calcium.* (Bull. de la Section Scientifique, v. 19. Académie Roumaine). Bucureşti, 1938.

« A pigeon injected (intraperitoneally) with „*Somatic serum*" ruffles its feathers, is lively, sometimes vomits, stands up and exhibits the « claspknife » movement of the wing; often the position of the wing is above the normal level. Frequently this pigeon also shows tremor. Such a pigeon is resistant to the action of chloroform, and in some cases the stimulation of sympathetic nerves was rapidly fatal ».

(Manuscript of the paper: *The sympathetic innervation of the skeletal muscle in the pigeon; its function and morphology*. 1929, p. 48)

(unpublished).

2. « Sympathetic innervation of the wing removed *in toto*. Somatic nerves to wing exercited faradically [1]) for 2—5—10 minutes, one off and on. Blood collected from the aorta into 3.8 p.c. sodium citrate (2: 1) and placed in ice-chest for 24 hours. This yields what may be called „*sympathetic serum*" » (Fig. 2).

(Physiol. Soc. Proceed. December 15, 1928).

« Intraperitoneal injection with „*Sympathetic serum*" produces depression of feathers; „slow-motion" wing; the pigeons become adynamic, tired and frequently sit down; sometimes they also show tremor. Such a pigeon is hypersensitive to chloroform and usually it dies on faradic stimulation of its somatic nerves ».

(Manuscript p. 48).

[1]) A Harvard induction coil actuated by a 2 volt accumulator and giving about 50 make and 50 break shocks per second, was used for the purpose of nerve stimulation. The electrodes were constructed of constantan resistance wire soldered to insulated copper wires, the latter being led through a pair of narrow bore glass tubes filled with paraffin wax and bound together. These tubes were drawn out to a fine point at one end and the constantan wire protruded only 1½ mm. The distance between the stimulating points was not greater than 0,5 mm. The strength of the stimulus was kept as constant as possible throughout all the experiments. The secondary coil was drawn away 12 cm. from the end and inclined at an angle of 45° to the primary coil. A very weak stimulus was thus produced and it seems very improbable that any spread of current could occur under these conditions.

B) *The possible explanation*

« By exciting one set or another of the nerves supplying the wing, we were able to change the composition and the properties of the blood in two opposite directions. The reactions to an injection of „*sympathetic serum*" are very similar to those resulting after injection of *Ringer solution* with calcium augmented. (Manuscript page 42). The reactions to an injection of „*somatic serum*" are similar to those of a injection with *Ringer solution* in which potassium is augmented.

(Manuscript, p. 42).

« In attempted explanation of this shift of reactivity following the excitation of somatic and sympathetic nerves the following suggestion is made: when one nerve supply to an organ is destroyed, e. g. the somatic, the excitation of the other, the sympathetic, leads to a disturbance of the ionic equilibrium, which can no longer be restored. The organ becomes ionically unbalanced. The whole body now exerts itself to restore the ionic balance in the unbalanced part, and produces a surplus of the necessary ions. Thus, for instance, in the case of the sympathetic serum, the sympathetic nerves to the wing having been ablated, excitation of the somatic nerves leads to an increase of K-ions which cannot be balanced by the destroyed sympathetic of the wing itself. This unbalanced liberation of K-ions demands an increase of Ca-ions which can only be produced by the combined action of the whole of the remainder of the sympathetic system. This in turn leads to an overproduction of *Ca* and the serum taken at this stage is called „sympathetic serum" because it contains an excess of *Ca* produced by overaction of the remainder of the sympathetic system.

« The opposite process must be assumed to be at work when we collected a „somatic serum", which after destruction of the somatic nerves to the wing and stimulation of the sympathetic nerves contains a larger amount of *K*

produced by the whole organism in response to the local perponderance of *Ca* in the unbalanced wing».

(Manuscript, p. 50—52).

II

1930

In collaboration with *Una Fielding*

«We have excited directly the highest splanchnic and somatic centres in the pigeon. In birds the motor cortex is located in the colliculi [1]) and the sympathetic centres are as usual in the hypothalamic region. Both regions are easily reached after opening of the skull and can be excited electrically. The procedure of excitation was the same as for the peripheral stimulation: 2—5—10 minutes excitation, one minute off and on. Blood was collected and treated as above.

«The serums showed again opposite effects on normal animals but the Sympathetic Central serum (after excitation of infundibulum) corresponds to the peripheral sympathetic serum obtained by excitation of somatic nerves in the absence of sympathetic; and the somatic central serum (collected after excitation of colliculi) corresponds to the peripheral somatic serum obtained by excitation of sympathetic in the absence of somatic nerves.

«It seems that the organism, when trying to reestablish the balance of ions, does so by involving in the reaction first of all the high antagonistic centres. For instance, when exciting somatic nerves after removal of the sympathetic, the high sympathetic centres (in the infundibular region), are in a state of hyperexcitation and they try to right the ionic balance by stimulating all the remaining sympathetic mechanism of the body. The overproduction of the local missing ion, effected through the central nervous mechanism, is easy to understand. In that way *the excitation of an important*

[1]) Gr. T. Popa and Florica Gr. Popa 1932: *Certain functions of the midbrain in pigeon.* (Proceed. of the Royal Society B. vol. 113, p. 191, 1933).

set of nerves to an unbalanced organ is equal to the direct central excitation of their antagonists » [1]).

(Manuscript. Additional, p. 1—3).

III

1929—1930

In collaboration with *R. Cernatescu*, Professor of Analytical Chemistry in the University of Jassy, Roumania, and *A. Meyer*, Assistant in Physical Chemistry at the same University

We have collected „*somatic*" and „*sympathetic*" serums from pigeons under the above described conditions and the chemical analyses were performed by *R. Cernatescu* and *O. Meyer*. The method of determination for *Calcium* was that of *Cramer-Tisdall* modified by *Clark-Collip;* and for *Potassium* the method of *Cramer and Tisdall* was used.

In a number of pigeons various injections with *K-Ringer* [2]) or *Ca-Ringer* [1]) were performed either intraperitoneally or intravenously, and serum collected and analysed as usual. The results are tabulated below:

A) The analysis made in 20 normal pigeons have yielded as an average content of *Potassium* and *Calcium* in the blood serum the figures:

K = 11—17 mgr. %; Ca = 9 — 11 mgr. %

B) *Somatic serums*

Pigeon 17	. . . . .	Ca = 12 mgr %
» 19	K = 47. 2 mgr %	. . . . .
» 21	K = 12.46 mgr %	Ca = 12.46 mgr %
» 23	K = 21. 7 mgr %	Ca = 14.15 mgr %

[1]) Although some authors admit the existance of parasympathetic centres in the hypothalamus *(Cushing)*, *Ranson* states as follows: « *...the hypothalamus is the chief centre for the sympathetic system* ». [*Some functions of the hypothalamus.* Bull. of the New-York Academy of medecine. Vol 13, pag. 241].

[2]) By these expressions we understand Ringer solutions in which the amount of potassium or calcium is increased.

Pigeon	25	K = 32. 3 mgr %	Ca = 13 mgr %
»	28	K = 14.44 mgr %	Ca = 8.58 mgr %
»	31	K = 14.95 mgr %	Ca = 13.95 mgr %
»	32	K = 17.69 mgr %	Ca = 9.86 mgr %
»	39	K = 17.30 mgr %	Ca = 10.93 mgr %
»	42	K = 31.47 mgr %	Ca = 11.07 mgr %
»	48	K = 23. 6 mgr %	Ca = 11.08 mgr %
»	50	K = 15.36 mgr %	Ca = 10.34 mgr %
»	52	K = 25.61 mgr %	Ca = 10.78 mgr %
»	54	K = 32.04 mgr %	. . . . .
»	57	K = 27.01 mgr %	Ca = 7.01 mgr %
»	60	K = 45.06 mgr %	Ca = 21.27 mgr %
»	63	K = 40.26 mgr %	Ca = 16.84 mgr %
»	107	K = 8.27 mgr %	Ca = 19.77 mgr %
»	182	K = 17.67 mgr %	Ca = 13.60 mgr %
»	215	K = 17.34 mgr %	Ca = 13.99 mgr %
»	218	K = 16.31 mgr %	Ca = 17.69 mgr %

C) *Pigeons injected with Ringer-K*

a) *intraperitoneally*

Pigeon	78	K = 33.25 mgr %	Ca = 18.45 mgr %
»	81	K = 19. 3 mgr %	Ca = 11.62 mgr %
»	87	K = 29.13 mgr %	Ca = 16.06 mgr %

b) *intravenously*

Pigeon	93	K = 18.52 mgr %	Ca = 12.41 mgr %
»	96	K = 27.17 mgr %	Ca = 27.46 mgr %
»	98	K = 12.52 mgr %	Ca = 32. 6 mgr %
»	102	K = 35.62 mgr %	Ca = 12.12 mgr %

D) *Sympathetic serums.*

Pigeon	16	K = 16.23 mgr %	Ca = 13. 7 mgr %
»	18	K = 24. 3 mgr %	Ca = 18. 7 mgr %
»	20	K = 17.75 mgr %	Ca = 13.75 mgr %
»	22	K = 37. 8 mgr %	Ca = 12. 8 mgr %
»	24	K = 11. 4 mgr %	Ca = 14. 5 mgr %

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Pigeon	26	K = 15.04 mgr %	Ca = 12.62 mgr %
»	29	K = 14. 5 mgr %	Ca = 10.16 mgr %
»	30	K = 10.34 mgr %	Ca = 9.65 mgr %
»	33	. . . . .	Ca = 10.06 mgr %
»	38	K = 14.24 mgr %	Ca = 12.02 mgr %
»	41	K = 18.73 mgr %	Ca = 14.42 mgr %
»	43	K = 9.65 mgr %	Ca = 17.92 mgr %
»	47	K = 32.92 mgr %	Ca = 17.78 mgr %
»	49	K = 13.77 mgr %	Ca = 12.38 mgr %
»	51	. . . . .	Ca = 11.15 mgr %
»	62	K = 26.00 mgr %	Ca = 12.18 mgr %
»	65	. . . . .	Ca = 12.82 mgr %
»	66	. . . . .	Ca = 19.93 mgr %
»	106	K = 19.38 mgr %	Ca = 13. 8 mgr %
»	181	K = 8.34 mgr %	Ca = 13.59 mgr %
»	214	K = 23.35 mgr %	Ca = 13.46 mgr %
»	217	K = 17.80 mgr %	Ca = 18.27 mgr %

E) *Pigeons injected with Ringer-Ca.*

a) *intraperitoneally*

Pigeon	77	K = 28.22 mgr %	Ca = 17.01 mgr %
»	80	K = 10.31 mgr %	Ca = 19.31 mgr %
»	83	K = 17.38 mgr %	Ca = 15. 9 mgr %
»	86	K = 26.58 mgr %	Ca = 16.98 mgr %
»	89	K = 11.71 mgr %	Ca = 13.45 mgr %

b) *intravenously*

Pigeon	92	K = 10.18 mgr %	Ca = 28.47 mgr %
»	95	K = 24.47 mgr %	Ca = 44.07 mgr %
»	97	K = 20.95 mgr %	Ca = 57.03 mgr %
»	103	K = 10.58 mgr %	Ca = 20.34 mgr %

By comparing the above figures one can draw the conclusions briefly summarized thus:

1. Excitation of one set of nerves always produces a disturbance in the K-Ca ionic balance of the blood serum.

This disturbance differs from one animal to another, the conditions of equilibrium in each one being probably different.

2. Generally the amount of *K* increases and decreases more markedly than the amount of *Ca*. Calcium seems to be more stable than potassium.

3. The change in the amount of one ion immediately provokes a change in the amount of the antagonistic ion. These two ions are always coupled [1]).

4. With some exceptions, it seems that in the somatic serums the *K* is increased more than *Ca*, whereas in the sympathetic serums *Ca* is more increased than *K*. If one takes into consideration the relationship between the two ions, one sees that the proportion of *K* in somatic serums is greater and, on the contrary, the proportion of *Ca* is greater in the sympathetic serums. At all events nerve excitations seem very readily to alter *K* and *Ca* follows so that *K* in these experiments shows the first change.

5. By injecting unbalanced Ringer solutions in the peritoneum or directly into the blood of pigeons the proper balance of the animal is still more disturbed, but in this case is seems that calcium becomes more mobile. Almost always it increases considerably if one injects either *Ringer-K* or *Ringer-Ca* [2]).

* * *

These results agree very well with those recorded under I, II, III.

---

[1]) See also R. Rosemann, 1922: *Über den Kalkstoffwechsel*. Arch. neerland. de Physiol. Vol. 7, p. 358.

R. Höber, 1920: *Zur Analyse der Calciumwirkung*. Pflüger's Archiv, vol. 182, p. 104.

[2]) Similar results obtained J. Toscano Rico, 1932: *Sur l'action hypercalcémiante des injections intraveineuses des solutions de KCl*. C. R. Soc. Biol., vol 110, p. 1056.

Further details in the paper: R. Cernătescu and A. Meyer: *Potassium et calcium dans le sang du pigeon après résection et excitation électrique des nerfs de l'aile*. Volume jubilaire en l'honneur du professeur Dr. C. I. Parhon, p. 131. Jassy-Bravo.

IV

1929—1930

In collaboration with *G. Tudoranu*, Professor of Medical Pathology in the University of Jassy

By excitation of antagonistic nerves of some important organ (such as the pigeon's wing) the ionic balance is altered and following it other properties of the blood are changed. In order to prove this, blood was taken in the same two opposite conditions described in the above experiments and was analysed by *G. Tudoranu* for:

a) *blood count;*
b) *refractive index;*
c) *albumins;*
d) *viscosity;*
e) *coagulation time.*

The results are tabulated below:

A) *Somatic Serums*

Anterior and posterior roots of the brachial plexus severed; sympathetic nerves of the wing excited faradically durnig ten minutes (fig. 3).

Pigeon	19	*a*	Before excitation	4.488.000
			After excitation	3.776.000
		b	A	35
		c	A	2.84
		d	A	1.1
»	23	*a*	B	4.344.000
			A	2.800.000
		b	A	40
		c	A	3.94
		d	A	1.2

Pigeon	25	*a*	B	4.520.000
			A	3.016.000
		b	B	40
			A	38
		c	B	3.94
			A	3.50
»	27	*a*	B	4.336.000
			A	3.000.000
		b	B	40.5
			A	36.0
		c	B	4.04
			A	3.06
		e	B	4 min.
			A	1 min.
»	124	*a*	B	3.272.000
				14.000
			A	2.790.000
				10.000
		b	B	39
			A	39
»	126	*a*	B	3.608.000
				8.000
			A	2.912.000
				8.000
		b	B	45
			A	45
»	132	*a*	B	3.520.000
			A	3.672.000
		b	B	41
			A	39.5
Pigeon	154	*a*	B	3.616.000
			A	3.384.000
		b	B	41.5
			A	40
»	207	*a*	B	2.800.000
				8.000
			A	2.408.000
				7.000
		b	B	43.5
			A	45
»	188	*e*	decreased	

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Pigeon 141	*a*	B	4.264.000	
			22.000	
		A	3.752.000	
			12.000	
	b	B		45
		A		43
» 186	*a*	B	3.088.000	
			5.000	
		A	2.688.000	
			4.000	

e Decreased.

B) *Pigeons injected with Ringer-K.*

a) *intraperitoneally*

Pigeon 81	*a*	B	3.624.000	
			10.000	
		A	3.596.000	
			9.000	
	b	B		39
		A		35
» 84	*a*	B	3.640.000	
			20.000	
		A	3.608.000	
			18.000	
	b	B		39
		A		34·5
» 87	*a*	B	4.328.000	
			14.000	
		A	3.664.000	
			8.000	
	b	B		30
		A		29

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b) *intravenously*

Pigeon	90	*a*	B	3.544.000
				8.000
			A	2.936.000
				4.000
		b	B	39
			A	38.5
»	93	*a*	B	3.848.000
				8.000
			A	3.804.000
				8.000
		b	B	39
			A	37
»	96	*a*	B	3.472.000
				12.000
			A	2.768.000
				4.000
		b	B	40.5
			A	38
»	98	*a*	B	3.336.000
				10.000
			A	2.064.000
				12.000
		b	B	35
			A	30.5
»	102	*a*	B	3.752.000
				18.000
			A	2.696.000
				8.000
		b	B	38
			A	33

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Pigeon 105	*a*	B	3.920.000
			8.000
		A	2.040.000
			12.000
	b	B	54
		A	40

C) *Sympathetic serums.*

Sympathetic chain of the wing removed; somatic nerves excited faradically during ten minutes (fig. 2).

Pigeon 18	*a*	B	1.528.000
		A	2.304.000
» 22	*a*	B	2.456.000
		A	4.526.000
	b	A	42
	d	A	1.2
» 24	*a*	B	3.936.000
		A	3.728.000
	b	B	50
		A	43
	c	B	6.12
		A	4.59
» 26	*a*	B	2.408.000
		A	3.858.000
	b	B	34.5
		A	32.5
Pigeon 106	*a*	B	3.836.000
			16.000
		A	4.048.000
			14.000
	b	B	40
		A	34
» 123	*a*	B	3.700.000
			10.000
		A	4.000.000
			10.000
	b	B	46
		A	43
» 206	*a*	B	2.488.000
			6.000
		A	3.656.000
			16.000

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	c	B	2.84	
		A	2.29	
	e	B	3 min.	
		A	7 min.	
Pigeon	38 *a*	B	3.456.000	
			20.000	
		A	4.000.000	
			22.000	
	b	B	42	
		A	37	
	c	B	4.37	
		A	3.28	
»	47 *b*	B	41	
		A	32	
	c	B	4.15	
		A	2.18	

e) increased.

D) *Pigeons injected with Ringer-Ca.*

a) *intraperitoneally*

Pigeon	77 *a*	B	3.512.000	
		A	3.900.000	
	b	B	34	
		A	34	
»	80 *a*	B	4.000.000	
			16.000	
		A	2.976.000	
			14.000	
	b	B	42	
		A	37	
	b	B	42	
		A	41	
Pigeon	181 *a*	B	3.504.000	
			7.000	
		A	3.872.000	
			9.000	
	b	B	44	
		A	40	

Pigeon 187 *e*) increased.

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Pigeon	83	*a*	B	3.320.000
				18.000
			A	3.720.000
				18.000
		b	B	44·5
			A	42
»	86	*a*	B	2.712.000
				8.000
			A	3.550.000
				20.000
		b	B	29
			A	27

b) *intravenously*

»	89	*a*	B	3.296.000
				12.000
			A	3.400.000
				20.000
		b	B	37
			A	33
»	92	*a*	B	3.720.000
				6.000
			A	4.080.000
				10.000
		b	B	38.5
			A	38.5
»	103	*a*	B	3.872.000
				14.000
			A	4.556.000
				22.000
		b	B	46
			A	45·5

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E) *Pigeons injected intravenously with various substances as controls.*

Pigeon 135 (10cc Hydrochl. Acid 2‰)	*a*	B)	3.872.000
			6.000
		A)	3.648.000
			4.000
	b	B)	40
		A)	40
» 137 (10cc Hydrochl. Acid 2‰)	*a*	B)	3.176.000
			16.000
		A)	3.328.000
			12.000
	b	B)	38
		A)	38
» 136 (Injected with $NaHCO_3$ 5%)	*a*	B)	3.084.000
			24.000
		A)	3.184.000
			16.000
	b	B)	48
		A)	46
» 139 (Injected with $NaHCO_3$ 5%)	*a*	B)	3.112.000
			18.000
		A)	3.048.000
			10.000
	b	B)	32.5
		A)	31.5
» 149 (Injected with alcohol 40% 1½cc)	*a*	B)	4.280.000
			16.000
		A)	3.240.000
			6.000
	b	B)	40
		A)	36.5

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Pigeon 150 (Injected with alcohol 40% 1½cc)

a	B)	4.248.000
		10.000
	A)	3.056.000
		2.000
b	B)	44
	A)	43

From the figures in the tables one may conclude:

1. Almost constantly the excitation of sympathetic nerves in the presence or (even better) in the absence of somatic nerves decreases the number of red corpuscles in the peripheral blood circulaiton, whereas the excitation of somatic nerves in the presence or (even better) in the absence of sympathetic nerves increases the number of red corpuscules in the peripheral circulation. A similar effect although not so constant is obtained with regard to the leucocytes [1]). It must be noted that merely cutting the nerves causes a change in the number of blood cells. When sympathetic nerves are severed the blood cells decrease in number and when the somatic nerves are cut the blood cells increase in number. This is just the opposite of the effects of stimulating the nerves.

2. Exactly the same effect is obtained by injecting intraperitoneally or (still more marked) intravenously *Ringer-Ca* or *Ringer-K*. In the first case the number of red corpuscles and leucocytes is increased whereas in the second the number of blood corpuscles and leucocytes decreases. Injections made, as control, with $NaHCO_3$ or HCl dit not change the number of blood cells. Alcohol injected intravenously always decreased the number of blood cells. These experiments show that the mere change of K-Ca balance changes also the distribution of cells by affecting probably the blood vessels innervation [2]).

[1]) Similar results obtained Fr. Czubalski, 1930: *Influence de l'excitation des nerfs pneumogastriques et sympathiques sur le nombre des plaquettes de Bizzozero et des leucocytes.* C. R. Soc. Biol. vol. 104, p. 899.

[2]) H. J. Hamburger, 1922: *Über die Bedeutung der Kalium und Calciumionen für das künstliche Ödem und für die Gefässweite.* Biochem. Zeitschrift, vol. 129, p. 153.
D. R. Hooker, 1911: *The chemical regulation of vascular tone as studied upon the perfused blood vessels of the frog.* Amer. Journ. Physiol., vol. 28, p. 361.

Invariably the time taken to effect coagulation of the blood is increased in the sympathetic serum, and decreased in somatic serum. This observation was noticed in the communication to the Physiological Society quoted above: « Somatic serum clears in 2—3 hours, transparent yellow, no diffusion of haemoglobin, no buffy coat, corpuscles deposited (Fig. 4 B.). „Sympathetic serum" coagulates, red colour, HC. diffuses, buffy coat most marked (Fig. 4 A). (Loc. cit. p. 11) [1]).

4. The albumins and the refractive-index of the serums *always decrease* after nerve excitations, no matter which of them is excited. The disturbance of ionic balance in favour of Potassium or Calcium is accompanied in either case by a reduction of albumins.

V

1930—1932

In collaboration with *Una Fielding*

All these experiments show that the shifting of K-Ca ionic balance plays a most important rôle in nervous activities and through nerves in all the important vital changes of the body.

In order to show the effects of too much *Ca* or too much *K* introduced by a natural way in the animal's body we have kept ten pigeons on a special water diet from July 29th 1930 until September 10th 1932.

One set of animals throughout this time drank a *Ringer-K* solution mixed with London tap water. The other set of pigeons had to drink a *Ringer-Ca* solution mixed with London tap water. The treatment of all the pigeons was exactly the same as usual and the only distinction between them and the controls (another set of pigeons) was the water for drinking.

Results. After two years of such a diet, *K-pigeons* showed: ruffled feathers, with a quick, brisk movement of the wing. They were lively and trembling almost all the time. Their

[1]) Similar results were obtained by J. Saulc, 1932: *Influence du système nerveux autonome sur la coagulation du sang*. C. R. Soc. Biol., vol. 110, p. 1101 and vol. 110, p. 1104.

movements in general were more rapid. Their feathers were not clean; the animals in general were very dirty. The faeces were watery and more or less coloured. They were apt to lose their feathers, which were very easy to pluck. Generally they showed difficulties in respiration. The females laid eggs and these eggs were normal in size or in some instances much larger (Fig. 5 a). The shells of the eggs showed a peculiar porosity and an uneven surface which sometimes was quite granular in aspect. The body weight decreased compared with the normal animals. The temperature remained normal.

When they were killed they showed the following peculiarities: they took chloroform quite well if care was taken with their difficult respiration. They did not sleep readily. During excitation the skeletal muscles showed great tremor. Electrical excitation of *somatic* nerves usually killed the animals in less than one minute. At the autopsy all the female *K-animals* showed well developed oviducts and a peculiar lack of fat (subcutaneous and perivisceral).

Ca-pigeons showed: depressed feathers close to the body; feathers were very clean and difficult to pluck. The birds' movements were slow, with a long contraction and idle flapping of the wings. They also showed tremors but not as markedly as in *K-pigeons*. Their faeces were of firmer consistency, whitish and not coloured. The respiration was normal and the females laid eggs with a definite decrease in size, which in some cases were not more than a quarter of the normal volume (Fig. 5 b). Some of them in addition to a great reduction in size, were devoid of yolk. The shell was very smooth and even, white and thicker than that of the potassium eggs. The body weight of Ca-pigeons was also decreased and in about the same proportion as in *K*-pigeons; but Ca-animals were more puffy, they looked bigger than *K*-animals, in spite of the weight being almost the same. The temperature was also normal.

When killed they took chloroform very badly, but they went to sleep very rapidly: in half to one minute the animals were under and if care was not taken they died suddenly.

Excitation of both somatic and sympathetic nerves were very dangerous and the animals died if subjected to continuous excitation. At the autopsy all the female animals showed well developed oviducts and a striking accumulation of fat subcutaneously and around the organs.

* * *

If one compares these results of experiments of long duration with those recorded under (I), one easily sees that it is an almost complete agreement between them. Excepting the behaviour of direct nerve excitation under chloroform all the other results which we found in 1927—29 were reinforced by the long water diet with unbalanced Ringer solutions [1]).

VI

1931—1932

In collaboration with *Florica Gr. Popa*, University of Jassy, and *Una Una Fielding*, University College of London

The discovery of „*hypophysio-portal*" vessels (Fig. 6) (which was recorded in „*The Lancet*" August 2nd 1930, and in „*Journal of Anatomy*" vol. 65, 1930) induced us to study more carefully the hypothalamic region (the region of high vegetative centres) and the hypophysis itself. Complete series of sections of human hypophysio-hypothalamic regions were made by *Florica Popa* in specimens of various mental conditions and cases in which death occurred in two opposite extremes, either violently or quietly. Some of the specimens were collected from the insane hospital in Jassy, some of them in the autopsy room of the laboratory of Legal Medicine of the same University. In addition, we controlled the facts on various normal series in embryos, still-born children, adult human beings, dogs, mice, birds and guinea-pigs.

[1]) See also the note: Gr. T. Popa and Una Fielding: *The influence of salt-balance upon the size of the eggs and nature of egg-shell in pigeons*. [Commemorative Volume «Grigore Antipa». Buc. 1938].

Especially useful were the extreme conditions in human subjects, which were found in:

1) two epileptics one of which died in seizure and the other by poison;

2) an intrasellar adenoma of the hypophysis;

3) a hypophysio-hypothalamus from a girl dead of leucaemia.

All these abnormal hypophyses showed some exaggerated morphological characters which we have seen many times in various degrees in the other series.

The first impressive character was that the sinusoids in the anterior lobe of the hypophysis and the hypophysio-portal vessels were in some instances full with red corpuscles (Fig. 7) in such tremendous amount that pressure is caused to the surrounding structures and they seem to occupy more than half the total surface of the section. The red corpuscles were pressed against one another so as to leave around them very little space, if any, for the blood plasma. In other instances, on the contrary, the sinusoids and hypophysial portal vessels are empty, shut up, and here and there one can see only ghosts of red corpuscles. In such cases the red corpuscles were definitely damaged: they seem to be squeezed, shrunken and often one could see only what was left after their destruction, a little remainder of the stroma. Undoubtedly *the red corpuscles were freely destroyed in the hypophysis and hypothalamus.* (Fig. 8). This destruction comes sometimes in waves. One sees in some hypophyses the periphery of the anterior lobe with empty sinusoids, with ghosts of red corpuscles and sometimes with colloid, and in other cases, on the contrary one sees the central sinusoids shut up and with destroyed red corpuscles inside, whereas the periphery is full of fresh and normal blood.

This picture of a concentration of red corpuscles in the hypophysio-portal vessels and sinusoids and their destruction is a new fact. It is of the utmost importance in the whole question of ionic balance. We leave aside the multiple implications of such a fact (which will be discussed in teh

paper containing the morphological evidence) [1]) and we only point here to the most important result: *one might consider the hypophysis as a potassium gland.* Indeed, by destroying red corpuscles, this gland possibly liberates *K-ions*, this compound being in great amount contained in the red cells. Subsequent experiments show that the destruction of red cells is not a brutal mechanical one, with liberation of the whole content, but a chemical process with liberation of some content of the cell, mostly K-ions, probably loosely bound to a more complicated body.

By such a mechanism the hypophysis continuously pours *potassium* into the hypothalamus, and in the cerebrospinal fluid.

This natural selection of a chemical compoud which is proivded directly to the central nervous system by an endocrine gland is extremely important. *Potassium* is an excitator of hypothalamic centres, whereas *Calcium* is an inhibitor of the same centres. The experiments of *Demole* [2]) (in which by injecting Ca Cl^2 solutions in the hypothalamic region one produces sleep and by injecting K Cl one produces states of excitation) agree entirely with our findings. Calcium is always present in small amounts in the cerebro-spinal fluid and also it is in comparatively large quantities in the blood serum. Potassium, on the contrary, is in small amounts in the blood serum, rich in spinal fluid and very rich in the

[1]) Details in the paper: Gr. T. Popa, *Le pouvoir hemoclasique de l'hypophyse.* Livre publié en hommage et dédié à la mémoire du professeur Cantacuzène. Masson et C-ie, 1934.

[2]) V. Demole, 1927: *Pharmakologisch-anatomische Untersuchungen zum Problem des Schlafes.* Arch. f. experim. Pathol. u. Pharmakol., vol 120, p. 229.

See also: M. Cloetta und H. Thomann, 1924: *Chemisch-physikalische Untersuchungen zur Theorie der Narkose.* Arch. f. Experim. Pathol. u. Pharmakol., vol. 103, p. 260.

H. Fischer, 1928: *Die Rolle des Calciums beim Zustandekommen von Narkose und Erregungszuständen am rindenlosen und am völlig dezerebrierten Tiere.* Arch. f. experim. Pathol. u. Pharmakol., vol. 138, p. 169.

F. Glaser, 1924: *Über psychophysische Reaktion.* Klinische Woch, p. 1493.

E. Brauchli und O. Schneider, 1926: *Über die Tonusverschiebungen im Blut bei Narkose und Erregungszuständen.* Arch. f. experim. Pathol. u. Pharm., vol. 119, p. 240.

S. Berggren und Erik Moberg, 1929: *Experimentelle Untersuchungen zum Problem des Schlafes.* Acta psychiatrica et neurologica, vol. 4, p. 1.

red corpuscles of the blood. When the need arises it may be delivered in large amounts directly to the hypothalamus by the hypophysis. For the function of the hypothalamic centres *Potassium* is absolutely necessary but it must not be in a too great amount (in that case it damages the nerve cells) and continuously it must be equilibrated by the antagonist ion, which for potassium, is more particularly *calcium* [1]).

But these two ions, on the other hand, show a different physico-chemical behaviour, which is very clearly shown also in our previous experiments (especially under III), namely: *calcium is slowly diffusible and is more difficult to eliminate, whereas potassium is very diffusible and ionises very easily* [2]). By this property we can better understand the hypothalamic activities as related to the sleep governing and wakening process in which this region is involved. The continuous pouring of potassium in the hypothalamic region maintains the nervous activity characteristic of the waking state. This continuous potassium flow into the brain necessitates the neutralisation of this ion, which, in itself and above a certain concentration, is dangerous for the same nervous system [3]). For this purpose calcium may be fixed by this region from the blood serum [4]) in greater quantities. But while potassium is easy to absorb through cell membranes and be neutralised, calcium diffuses very slowly and accumulates. This accumulation of calcium in the hypothalamus causes the tired state of the brain and in consequence induces sleep. During sleep, potassium would not be poured in the same amounts as in the waking state into the hypothalamus and the calcium surplus can be eliminated little by little,

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[1]) See: P. Gerlach, 1914: *Der Einfluss verschiedener Ionen auf das Überleben des Zentralnervensystems von Säugetieren.* Biochemische Zeitschrift, vol. 61, p. 125.

[2]) See: Carlson, 1906: *The specific influence of the inorganic salts of the blood on the heart ganglion and the heart muscle.* Amer. Journ. Physiol., vol. 16, p. 386.
R. W. Webster, 1927: *Potassium and tartrates. A review of the literature on their physiological effects.* Chicago.
C. P. Stewart and G. H. Percival, 1928: *Calcium and Metabolism.* Physiol. Reviews vol. 8, p. 283.

[3]) Probably in the process of calcium-ions shifting play a certain role also the pineal gland.

[4]) P. Gerlach *loc. cit.*

until again a proper balance for the waking state is reached [1]).

The pouring of potassium itself in the brain is probably regulated by a fine mechanism in the following way:

The hypophysio-portal vessels carry their content partly in the supraoptic and paraventricular nuclei. These nuclei send nerve fibres along the hypophysial stalk to the posterior lobe and pars intermedia [2]). Some authors have seen nerves penetrating into the anterior lobe itself, how far is uncertain. It is probable that these fibres somehow reach the hypophyseal arteries or the hypophysio-portal vessels, the diameter of which they regulate. If we suppose that K-ions excite the neurones of the supraoptic and paraventricular nuclei and Ca-ions inhibit them (as these ions do in the other parts of the brain) then the regulating mechanism of potassium rate for the brain is easy to understand. Namely, a great amount of potassium would excite the neurones of those two nuclei, excitation which will close the lumen of hypophyseal arteries or of hypophysio-portal vessels. This action will be followed by an accumulation of calcium, which still is carried to the above mentioned nuclei by the blood

[1]) See: C. v. Economo, 1929: *Schlaftheorie*. Ergebn. der Physiol. vol. 28, p. 312.
W. R. Hess, 1931: *Le sommeil*. C. R. Soc. de Biol. vol. 107, p. 1333. In the discussions at the meeting of the « *Société de Biologie* », Bremer expressed himself in the following words: « If the sleep is caused by an inhibition this must be of a very different kind, which is not similar to the usual nervous inhibition which lasts only a few seconds. Either it is an inhibition of a physical state, *or the inhibitory cause is a substance which disappears slowly* ».
N. Kleitmans, 1929: *Sleep*. Physiological Reviews, vol. 9, p. 624.

[2]) Cajal, Ramon y., 1894: *Algunas contribuciones al conocimento de los ganglios del cerebro*. III. *Hypophysis*. Ann. Soc. espan. Histor. natur. Ser. 2, vol. 3.
Dandy W. E., 1910—1911: *The nerve supply of the pituitary body*. Amer. Journ. Anat.
Gentes L., 1903: *Terminaisons nerveuses dans le feuillet juxta-nerveux de la portion glandulaire de l'hypophyse*. C. R. Soc. Biol., vol. 55, p. 336.
Greving R., 1926: I. *Beiträge zur Anatomie der Hypophyse und deren Funktion*. II. *Das nervöse Regulationssystem des Hypophysen-Hinterlappens (Der Nukleus supraopticus und seine Fasersysteme)*. Zeitschr. f. d. gesamte Neurol. u. Psych., vol. 104, p. 466.
Pines, J. L., 1925: *Über die Innervation der Hypophysis cerebri*. Zeitschr. f. d. gesamte Neurol. u. Psych., vol. 100, p. 123.
Berkely H. J., 1894: *The finer Anatomy of the infundibular region of the cerebrum, including the pituitary gland*. Brain., vol. 17, p. 515.
Tello F., 1912—1914: *Algunas observaciones sobre la histologia de la hipofisis humana*. Trabajos del Lab. de investig. biologicas., vol. 10, p. 145.

plasma of the systemic arteries. This accumulation of calcium would in its turn inhibit the same neurones and open again the channels for potassium flow. This neuro-humoral mechanism for regulating the K-Ca ratio for the hypothalamus, is of the greatest delicacy and includes in itself a large range of possibilities for varying smoothly, in the way characteristic of every biological process.

If this hypophysio-hypothalamic mechanism is admitted, then it must be involved in every change which takes place at the periphery. We find here a highly organised mechanism for balancing ions (in first place Ca-K). This supreme mechanism is working on the base of a material prepared by the whole organism. The hypophysio-hypothalamic mechanism is working by using blood and this blood is variously balanced by the activities of the other organs.

The various organs of the body have a different content of potassium and calcium and certainly they have a various balance of ions. So for instance the skeletal muscle is very rich in potassium [1]); liver and spleen are also rich in potassium [2]); intestines and genital organs have much calcium [3]); brain [4]) and cerebro-spinal fluid [5]) contain also much potassium; the heart has conspicuous amounts of both compounds. Supposing that in some individuals the systemic blood is more balanced in favour of calcium, the hypophysio-hypothalamus regulating mechanism will have to work on a blood already disbalanced and its potassium providing

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[1]) Katz, 1896: *Die mineralischen Bestandteile des Muskelfleisches.* Pflügers Arch., v. 63, p. 1.

F. Urano, 1907: *Neue Versuche über die Salze des Muskels,* Zeitschr. f. Biol., vol. 50, p. 212.

[2]) Denstedt und Rumpf, 1905: *Weitere Untersuchungen über die chemische Zusammensetzung des Blutes und verschiedener Organe.* Zeitschr. f. Physiol. Chem., vol. 23, p. 483.

[3]) T. Saiki, 1908: *A chemical study of non-striated mammalian muscle.* Journ, of. biol. Chem., vol. 4, p. 483.

[4]) Macallum, 1908: *Die Methoden und Ergebnisse der Mikrochemie in der biologischen Forschung.* Ergebn. der Physiol., vol. 7.

Albu-Neuberg, 1906: *Mineralstoffwechel,* Berlin.

Thudichum, 1901: *Die chemische Konstitution des Gehirns des Menschen und der Tiere,* Tübingen.

[5]) E. Newratski, 1897: *Zur Kenntnis der Cerebrospinal-Flüssigkeit.* Zeitschr. f. physiol. Chem., vol. 23, p. 532.

power will be more incited to work. On the contrary in some other persons we might have a blood in which the balance favours potassium, and in this case the hypophysio-hypothalamic regulating mechanism will have to work on a blood disbalanced in favour of potassium and its calcium providing power can be increased by simply shutting the potassium channels.

The same change in the activity of the hypophysio-hypothalamic mechanism, certainly must be at work in one and the same individual at various periods of his life. There are periods in which the blood is unbalanced towards potassium-plenty and others in which the blood is unbalanced towards calcium-plenty.

* * *

Up to now we have considered the conditions in the organism somehow schematically. But the balancing power of the organism is still finer than we have imagined. There is not only a *single* balance Calcium-Potassium, but an infinity of them ranged between a *maximum* and a *minimum*. According to *Neuschlosz* [1]) 1K Cl can be equilibrated by 1/20 Ca Cl_2 and conversely 1 Ca Cl_2 can be also equilibrated by 1/20 K Cl. Between these extremes all the intermediate quantities equilibrate each other. And if we take into consideration that there are not only two ions at work in the blood serum, and that a whole series of the intermediate chemical compounds interferes, we understand how extremely delicate and multiple are the posibilities of the organism to disturb and to right again the ionic balance in the blood, and we can see also that there are states of disturbed balance of ions which do not appear as such for the usual observation merely because they did not reach either the maximum nor the minimum of the balancing power.

We might conclude: « This theory is probably too simple and the reality far more complicated. We do not know if

[1]) S. M. Neuschlosz, 1920: *Die kolloidchemische Bedeutung der physiologischen Ionen-Antagonismen und der equilibrierten Salzlösungen.* Pflügers Arch., vol. 181, p. 17.

we are dealing only with a disturbance of the ionic-equilibrium followed by the balancing effort of the organism or if there are also some excitatory substances or „chemical messengers" resembling hormones. As a matter of fact we have observed that the effects of Ca- and K-Ringer injections do not last as long as the effects of the corresponding sera and that the effect of either Ringer solution is much increased by combining it with the appropriate serum. This suggests the probability of there being present in the sera not only a disturbance of the Ca-K balance, but also some substances which are able to prolong the effects of such a disturbance » [1]).

(Manuscript p. 51).

VII

1935—1938

Ions, Erythrosoma and *Cerebrostimuline*

We have seen in chapter VI that in the hypophyseal gland red corpuscles are destroyed and we have advanced the hypothesis that the pituitary is a potassium producer for the brain. This supposition is now a certainty [2]). We have found in the cerebrospinal fluid a very exciting residue which contains a great amount of potassium. This residue was called temporary „cerebrostimuline" [3]). One finds always the exciting substance in greatest concentration in the third ventricle of the brain and less concentrated everywhere in the spinal fluid. With the residue of cerebrospinal fluid one obtains exactly the same kind of central nervous excitation as with a potassium chloride solution. This excitation is a

[1]) Answering to a question of Demole, Hess (at the meeting of « Société de Biologie » *(l. c.)* said: « We are dealing here with a series of mechanisms which are linked with the alterations of the activity in the whole body and, no doubt about, the K-Ca equilibrium play a very important rôle in them. But we must also account for a hormonal mechanism on which we still are as yet very little oriented ».

[2]) Gr. T. Popa: *Neurotropic principles in the sheep hypophysis including a « cerebrostimuline »*. Academia Română. Mem. Sed. Ştiinţ. Seria III. Tome XIII, Mem. 6, 1938.

[3]) Popa, Lucinesco, Wasserman et Gheller: *La cerebrostimuline telle qu'on la connait aujoud'hui*. Acad. Rom. Mem. Sect. Ştiin. Seria III. Tome XIV. Mem. 8, 1938.

tetanizing one, leading to a contracture of the whole musculature and it is, after all, the exageration of the usual exciting effect of potassium, which was found in the so-called „somatic-serum". (See chapter I). The effect of cerebrostimuline is removed by calcium-chloride, which, injected in the brain cavities, shows an intense depressive power. We find here, therefore, the same general antagonism between potassium and calcium. In connection with some of our recent experiments we believe that someway the pineal gland could be the provider of calcium-ions for the diencephalon as the hypophysis is a provider of potassium-ions for the same part of the brain. One of these endocrines would be a natural excitator of the brain („cerebrostimuline") and the other would be a natural depressor of the brain („cerebrorelaxine"). By their fine equilibration it would be determined the general behavior of diencephalon and of the brain, especially the ciclic activity resulted in sleep and weakness.

We ignore, as yet, the source of calcium in its relation with the pineal gland; but we have strong reasons to believe that the red corpuscles of the hypophyseal blood are the source of potassium found in the cerebrospinal fluid. Looking for the mechanism of potassium elimination in this fluid, we have found the peculiar intravascular destruction of red cells, mentioned in chapter VI [1]). This destruction is preceded by a well-known deformation of red-cells which become prickly and little by little they detach their spikes abandoning them in the surrouding medium. This distortion process of the red corpuscles is highly increased by exciting electrically the nerves and we obtain the numerous spikes, eliminated after excitation, as a fine upper-layer in the sedimentig blood (Fig. 9).

Such detached particles of the red cells are scattered in the blood serum (Fig. 10) and what is more important they are found in nearly all the endocrine glands. We have seen them in the hypophysis (Fig. 11) in the suprarenal gland (Fig. 12), parathyroids, carotid corpuscle, pancreatic islets.

[1]) Details in the paper: Gr. T. Popa: *La desintégration de l'hematie*. Annales de Médicine. Tome. 41, pag. 235., 1937.

The peculiar slow circulation, under a low pressure of the sinusoidal blood in the endocrines, with free communication to the glandular celles, facilitates the distortion of the red cells and the elimination of spikes. These are used by the glandular cells which phagocytize them. As for the moment we cannot distinguish between the various particles separated from the red cells and as they are found everywhere in the blood and in the endocrine glands, we believe that it is necessary to give them a certain name and we shall call them „*erythrosoma*", meaning by this: *particles separated from the red cells of the blood.* The erythrosoma are minute bodies which, considernig their size, are placed between cells and granula.

Summing-up the conclusions of our research work from 1927 up to now, we may say that we have established a certain relation between the nerve activities, the equilibrium of potassium calcium ions and the red blood cells. Nerve excitations change the balance of ions and this, in turn, modifies the shape of red cells which give up some of their material (erythrosoma) used afterwards by the endocrine glands. The equilibration of ions is universal in the organism and it is very finely performed in the blood serum in which there is great tendency to maintain a certain salt balance. This fine balancing of ions can be strongly influenced by a central mechanism placed in diencephalon where a greater change in the amount of K. or Ca.. leads to central hyperexcitation or central depression and in this way the composition of the whole blood serum tends to be changed. One can establish, therefore, a close material relation between nerves, red cells and endocrines, which are working together.

BCU IASI

EXPLANATION OF FIGURES

Fig. 1. — Diagram representing the brachial plexus [BR. PL.] of the pigeon in relation with the sympathetic chain [Sy.]. There is a close relation between these two parts of nervous system, but with a fine ophthalmic knife one can easily separate them from each other and excite them in turn.

Fig. 2. — Diagram of brachial plexus in pigeon excited with two electrods [E] in the absence of sympathetic chain, which was previously removed. In such circumstances the wing of the bird, including the large mass of pectoralis muscle, is unbalanced. For the defective sympathetic nerves of the operated wing, react, against an electric excitation of the somatic nerves, the whole remainder of the sympathetic system of the body. This reaction overpass the local needs and that is the reason why the effect of a somatic nerve produces a modification of the blood-serum similar to that caused by the direct excitation of the sympathetic in the presence of the untouched somatic nerves. In the case of the excitation of somatic nerves after removal of sympathetic we expected to find more potassium in the blood serum and somatic effects after injection to another animal of such a serum; instead of these expectations we have found an augmentation of calcium in the serum and we have obtained sympathetic effects injecting the serum to another animal. On the contrary, we have obtained increase of potassium in serum when the excitation of somatic nerves of the wing was performed without removig previnsly the sympathetic nerves. Potassium also was increased when the high somatic centres (colliculi) were excited. In such circumstances there is no other explanation for the reversal of the effect in the unbalanced organs than the reaction of the whole organism for the defecting part. Such reactions are always « *overreactions* » with excessive production of the missing factor.

Fig. 3. — Diagram of the sympathetic chain of the wing in pigeon, excited with two electrods [E] in the absence of somatic nerves which were previously severed. In this case the wing and the pectoralis muscle are unbalanced in the reverse way: the respective brachial plexus cannot react when its antagonist (sympathetic of the wing] is excited. For the defective somatic nerves of the wing reacts the remainder somatic system of the body. As a result we have found in the blood-serum an excess of potassium although we expected to find excess of calcium, which always occurs when we excite sympathetic in the presence of its antagonist (somatic nerves). The explanation of this reversed effect is of the same kind as in fig. 2. For these reasons we have called « *sympathoserum* » either a blood-serum collected after direct electric excitation of sympathetic in the presence of untouched somatic nerves, or of blood-serum collected after excitation of somatic nerves, its sympathetic antagonist benig previously removed. For the same reasons we have called « *somatoserum* » either a blood-serum collected after direct excitation of somatic nerves in the presence of untouched sympathetic, or of blood-serum collected after excitation of sympathetic nerves their somatic antagonist being removed.

Fig. 4. — A) A glass tube in which one sees how is looking like a sympathoserum prepared by a treatment diagramatically represented in fig. 2. In such a serum calcium is augmented, the coagulating power increased and there is haemoglobin diffusion. Injected to another animal it shows nervous depressing capacities.

B) Second glass tube in which there is a somatoserum prepared according to the diagram in fig. 3. In such a serum potassium is increased. There is neither

coagulation nor haemoglobin diffusion. The red cells are all deposited. Injected to another animal this serum shows nervous exciting power.

Fig. 5. — *a)* Pigeon-eggs laid by animals kept on a special hydric diet in which potassium was in excess. The experiment continued over two years (since July 29th 1930 to September 10th 1932). The eggs were large, with thin and porous shell.

b) Pigeon-eggs laid by animals kept on a special hydric diet in which calcium was in excess. Experiment of the same length of time. The eggs were small, with thick and shiny shell. It is to be noted that in this experiment calcium vas in greater proportion than it is usually in a tap-water (in *a* — series of birds) and in series *b* of pigeons potassium was also in larger amount than it is in tap-water. The animals drank Ringer solutions, in which one ($K^{\cdot}$) or the other ion ($Ca^{\cdot\cdot}$) was increased. Therefore, the porosity of shells in the case *a* is not due to lack of calcium and the smallness of eggs in *b* is not due to lack of potassium. The absolute quantity of each salt is sufficient for a normal production of eggs, only the relative proportion of two ions [$K^{\cdot}/Ca^{\cdot\cdot}$] is changed.

Fig. 6. — Photograph of a still-born child hypophysis cleared in xylol. One can see in the picture a black portion of the gland which is the anterior lobe. Behind, one can see the posterior lobe which is clear and continous with the hypophyseal stalk. Above the stalk there is the hypothalamus looking like a funel. In front of the stalk the hypophyseo-portal vessels ascend towards the third ventricle's recess and towards hypothalamus. One of these vessels reach a very high position of the infundibulum.

Fig. 7. — Magnification of a fragment from anterior lobe. Four large vessels (sinusoids) are full of red cells which are so crowded that they press to each other. They look like a squized mass of globules left without any space around, the surrouding fluid being pushed away in some other parts of the vascular system.

Fig. 8. — Hypophysis of adult man. Section through anterior lobe. Three large sinusoids are seen full with distorded red cells. Here and there some of the corpuscles are still intact. The majority of red cells are prickled and around them there are crowds of erythrosoma detached. *C* = globules of colloid.

Fig. 9. — Glass tubes containing blood, taken from rabbits in which somatic or sympathetic nerves were electrically excited. One sees above the red cells deposit a white layer in which we find by staining bodies like those represented in fig. 10. These are spikes detached from the red cells, which we have called erythrosoma. We ignore, as yet, the nature of these fragments of red cells. They might be simply lipoid globules separated from the red cells, or more complicated parts of the red cells given up to the surounding medium in certain conditions. A kind of such separation between the red cells and erythrosoma, as we see in a glas tube, might be produced in different ways and various proportions in the endocrine glands where the circulation is slow and the blood pressure low. These erythrosoma are very easily phagocytised by the white cells of the blood and also by the endocrine cells, especially those of hypophysis and suprarenal. The erythrosoma are especially numerous after nervons excitation and after change in the relation of certain ions ($K^{\cdot}/Ca^{\cdot\cdot}$). We believe, therefore, that every nerve excitation changes the ionic-balance in the blood-serum and this change, in turn, leads to distortion of red cells with elimination of erythrosoma. Such elimination is especially intense in the endocrine glands, where the mechanical conditions of circulation are more favorable.

Fig. 10. — Erythrosoma stained with haematoxylin-eosin. They were taken from the white layer of the glas tubes in fig. 9.

Fig. 11. — Hypophysis of dog excited with cerebrostimuline. Microphotograph [Ob.D. × Oc.K^1] of a section through the anterior lobe. A large sinusoid full with erythrosoma.

Fig. 12. — Microphotograph, on dark field, of a drop of blood, taken in the central blood vessel of a guinea-pig suprarenal. One can see prickled red cells and around them numerous erythrosoma. Looking carefully one can follow sometimes under the microscope the actual separation of erythrosoma from the red cells.

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Fig. 1. — The relation of sympathetic chain (Sy) with the brachial plexus (Br. Pl.) in pigeon.

Fig. 2. — Sympathetic chain removed. The somatic nerves of the brachial plexus excited.

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a b

Fig. 5

Fig. 3.— Somatic nerves of the brachial plexus severed. The sympathetic chain excited.

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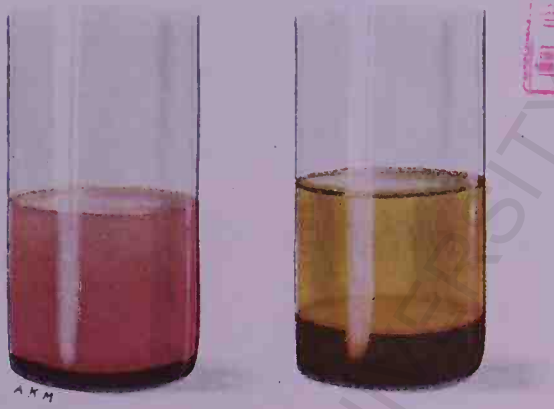

Fig. 4.

Pigeon 283. Serum prepared as follows: sympathetic chain of the left wing removed and somatic nerves excited faradically 10 minutes. Sodium citrate used. Sketch made after 48 hours. Serum as jely, bloodcelles not deposited in the whole. Serum shows the properties of a Ca-Ringer solution.

(Sympathoserum)

(August 31. 1928.)

Pigeon 284. Serum prepared as follows: anterior and posterior roots of the left brachial plexus severed. Leftsympathetic nerves of the wing excited faradically 10 minutes. Sodium citrate used in the same proportions as for pigeon 283. Sketch after 48 hours. Serum perfectly clear; all blood cells deposited. Serum shows the properties of a k-ringer solution.

(Somatoserum)

(August 31. 1928.)

The blood was kept in refrigerator.

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Fig. 6

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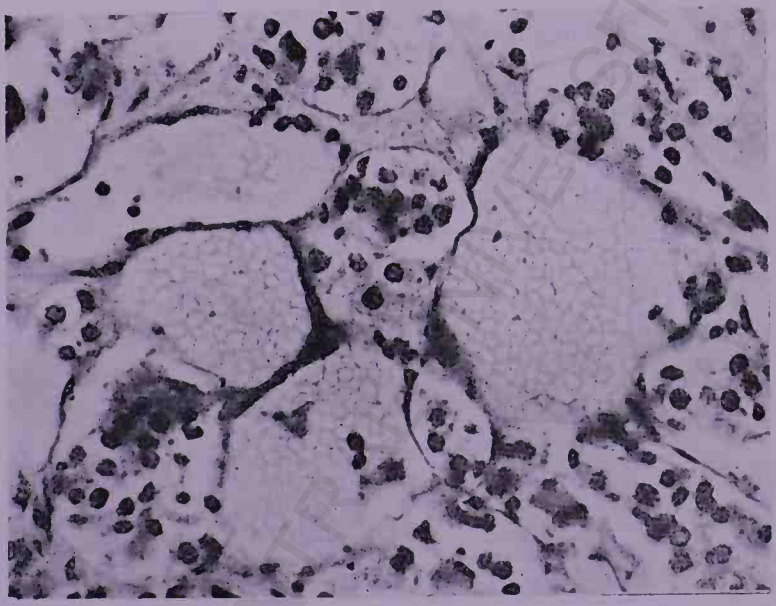

Fig. 7

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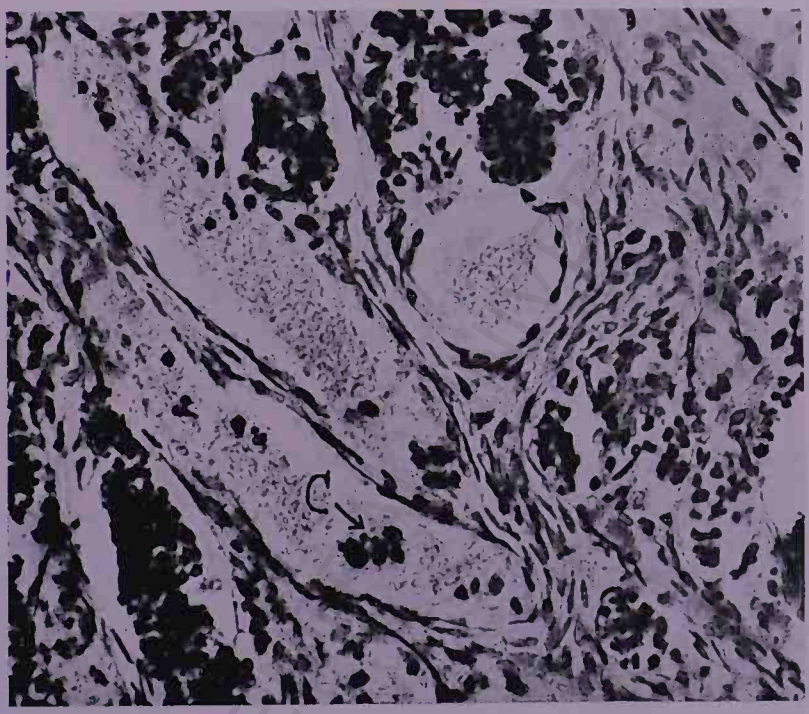

Fig. 8

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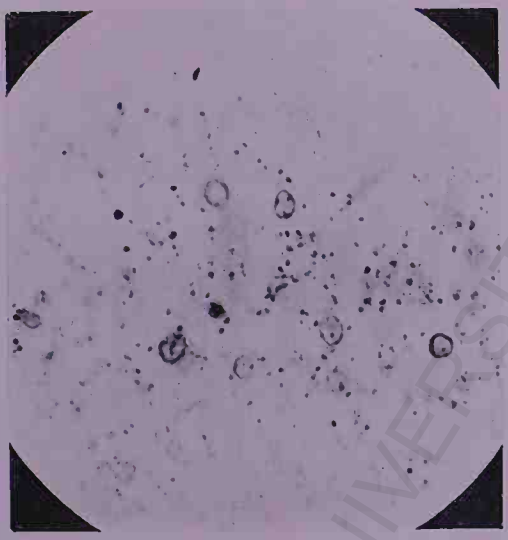

Fig. 10.

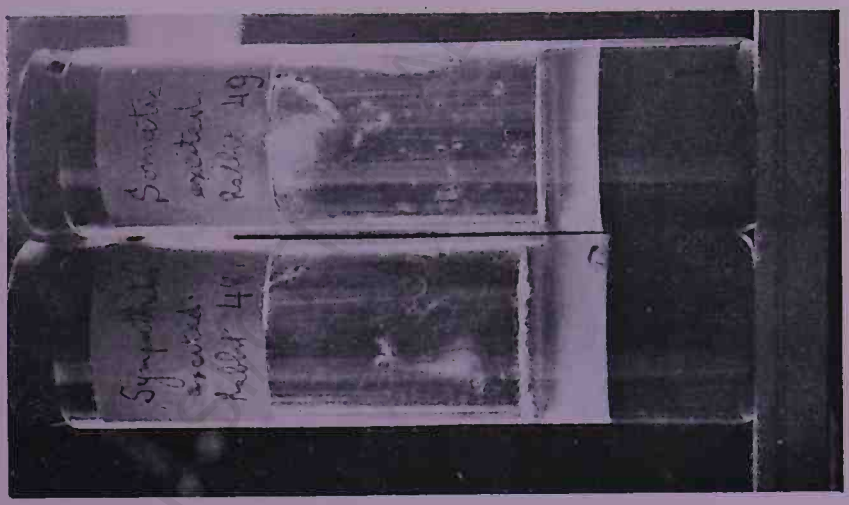

Fig. 9

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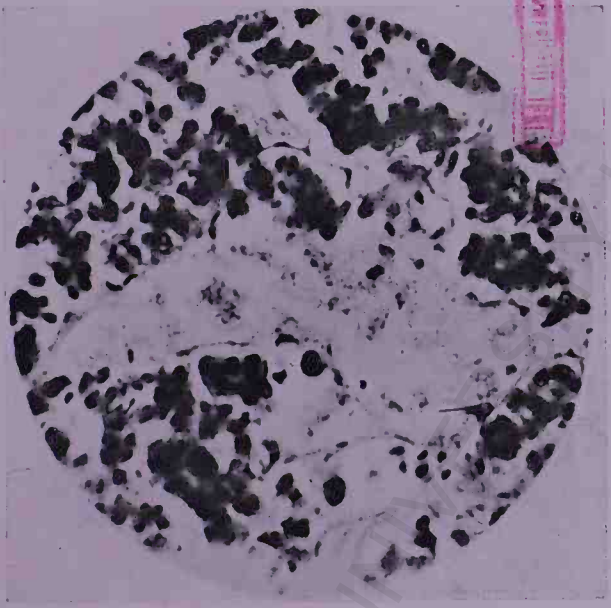

Fig. 11

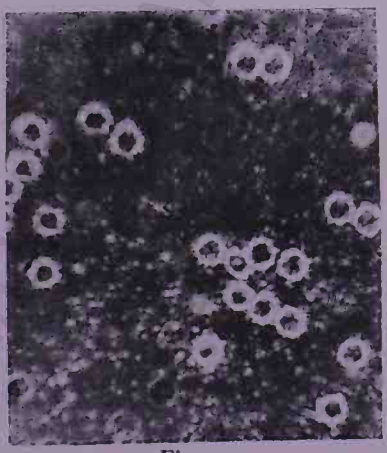

Fig. 12

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